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Effect of 2 percent Venous Carboxyhemoglobin on Exercise-Induced Angina Pectoris

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EFFECT OF 2% VENOUS CARBOXYHEMOGLOBIN ON EXERCISE-INDUCED ANGINA PECTORIS

by

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16. ABSTRACT

In a double-blind, randomized, crossover study, 15 patients with angina pectoris who breathed carbon monoxide 50 ppm for 1 hour to raise the mean venous carboxyhemoglobin from 1.09 to 2.02% had a reduction in mean exercise time until angina pectoris from 321.7 to 289.2 seconds, $P<0.001$. After breathing compressed, purified air to reduce the mean venous carboxyhemoglobin from 1.07 to 1.00%, there was an insignificant increase inmean exercise time until angina pectoris from 324.5 to 330.3 seconds. Incomparison with the control period or after breathing compressed purified air, a 2.02% venous carboxyhemoglobin level caused a reduction in exercise time until angina pectoris, $P<0.001$, no significant change in resting sytolic blood pressure times heart rate, a reduction in systol blood pressure times heart rate at angina pectoris, $P<0.001$, and no significant change in exercise-induced ischemis S-T segment depression. These data indicate that a 2% venous carboxyhemoglobin level aggravates angina pectoris.

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FOREWARD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This study assesses the associated risk of carbon monoxide exposure on a susceptable population, subjects with angina pectoris, secondary to coronary heart disease.

Results from this study will provide additional information on the dose-effect relationship of carbon monoxide exposure and would be of importance in the review and revision of the national air quality criteria for carbon monoxide.

F. Gordon Hueter
Director
Health Effects Research Laboratory

ABSTRACT

In a double-blind, randomized, crossover study, 15 patients with angina pectoris who breathed carbon monoxide 50 ppm for 1 hour to raise the mean venous carboxyhemoglobin from 1.09 to 2.02% had a reduction in mean exercise time until angina pectoris from 321.7 to 289.2 seconds, $P<0.001$. After breathing compressed, purified air to reduce the mean venous carboxyhemoglobin from 1.07 to 1.00%, there was an insignificant increase in mean exercise time until angina pectoris from 324.5 to 330.3 seconds. In comparison with the control period or after breathing compressed, purified air, a 2.02% venous carboxyhemoglobin level caused a reduction in exercise time until angina pectoris, $P<0.001$, no significant change in resting systolic blood pressure times heart rate, a reduction in systolic blood pressure times heart rate at angina pectoris, $P<0.001$, and no significant change in exercise-induced ischemic S-T segment depression. These data indicate that a 2% venous carboxyhemoglobin level aggravates angina pectoris.

This report was submitted in fulfillment of Interagency Agreement EPA-80-D-X0921 by the Veterans Administration Hospital, Long Beach California under the sponsorship of the U. S. Environmental Protection Agency. This report covers the period December 1, 1979 to November 30, 1980 and work completed as of March 17, 1980.

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SECTION 1

INTRODUCTION

Exposure to carbon monoxide from smoking or heavy atmospheric carbon monoxide pollution impairs cardiovascular function in patients with cardiovascular disease (1-14), in patients with chronic obstructive pulmonary disease (15), and in normal persons (16-18), and reduces ventricular fibrillation threshold in dogs with acute myocardial injury (19) and in normal dogs (20). Exposure to carbon monoxide from smoking or heavy atmospheric carbon monoxide pollution depresses myocardial function in patients with coronary heart disease (1, 2, 10), causes a reduction in exercise time until the onset of angina pectoris in patients with coronary heart disease (4-7, 9, 11, 12, 14), and causes ischemic ST-segment depression $\geq$ 1.0 mm after exercise-induced angina pectoris to occur earlier and after less exertion (4-7, 9, 11, 12, 14).

Two double-blind, randomized studies have confirmed that exposure to carbon monoxide in concentrations found during heavy atmospheric carbon monoxide pollution aggravates exercise-induced angina pectoris (6, 7). Anderson and associates documented in a double-blind, randomized study that patients with angina pectoris who breathed carbon monoxide 50 ppm intermittently for 4 hours to raise their mean venous carboxyhemoglobin level from 1.3% - 2.9% had a decrease in exercise time until the onset of angina pectoris compared with that observed after breathing compressed, purified air (6). Exposure to carbon monoxide caused deeper ST-segment depression during and after exercise in five of their 10 patients, with earlier onset and longer duration of ST-segment depression.

We demonstrated in a double-blind, randomized study that patients with angina pectoris due to documented coronary artery disease who breathed 50 ppm of carbon monoxide for 2 hours to raise their mean venous carboxyhemoglobin level from 1.03% - 2.68% had a 16% reduction in mean exercise time until the onset of angina pectoris and a decrease in the product of systolic blood pressure times heart rate at the onset of angina pectoris (7). Ischemic ST-segment depression $\geq$ 1.0 mm after exercise-induced angina pectoris occurred earlier, after less exertion, and at a lower product of systolic blood pressure times heart rate at the onset of angina pectoris after exposure to carbon monoxide compared with the control periods or with the periods after breathing compressed, purified air.

It was recently demonstrated that exposure to passive smoking aggravates exercise-induced angina pectoris (12). The mean venous carboxyhemoglobin level observed after exposure to passive smoking in a well ventilated room was 1.77% and after exposure to passive smoking in an unventilated room was 2.28%. However, it should be emphasized that in addition to carbon monoxide, nicotine, other components of tobacco smoke, including oxides of nitrogen, and possibly psychological factors may have contributed to the decrease in exercise performance observed in the patients with coronary heart disease after exposure to passive smoking.

Two double-blind, randomized studies (6, 7) have confirmed that venous carboxyhemoglobin levels of 2.5% - 3.0% aggravate angina pectoris secondary to coronary heart disease. It would be important to determine

in a double-blind, randomized study whether a venous carboxyhemoglobin level of 2% does or does not aggravate exercise-induced angina pectoris.

SECTION 2

CONCLUSIONS

Breathing carbon monoxide to raise the venous carboxyhemoglobin level from 1% to 2% aggravates angina pectoris due to coronary artery disease. If there is a safe threshold level of carbon monoxide exposure for patients with angina pectoris due to coronary artery disease, this level would have to be very low.

SECTION 3

RECOMMENDATIONS

On the basis of the medical data from this research study, there should be no relaxation of the present U. S. Environmental Protection Agency Air Quality Criteria for Carbon Monoxide.

SECTION 4

MATERIALS AND METHODS

Fifteen patients, 14 men and one woman, mean age 59.0 ± 7.2 years, with stable angina pectoris due to angiographically documented coronary artery disease were subjects. Eight of the 15 patients (53%) also had a previously documented healed myocardial infarction. None of the 15 patients were smokers or had anemia. Written informed consent was obtained from all.

The patients were brought to the cardiovascular laboratory and familiarized with the equipment and the procedures before the study was done. They practiced exercising upright on a Collins constant load bicycle ergometer before the study was done.

On two successive study mornings, at 8 a.m., with the subject in the fasting state, venous blood was drawn and analyzed for carboxyhemoglobin and hemoglobin levels (and for methemoglobin levels in the last eight patients) with a 282 Co-Oximeter (Instrumentation Laboratory, Inc.). The 282 Co-Oximeter was calibrated daily according to the instructions on pages 5.1 and 5.2 of its Operator's Manual (21).

Simultaneous leads II and V_5 were then recorded with an electrocardiograph with the patient sitting on the bicycle ergometer. The resting heart rate was obtained from this electrocardiogram. The resting blood pressure was next measured with a mercury sphygmomanometer. Each subject then exercised upright on the bicycle ergometer with a progressive work load until the onset of anginal discomfort, and the duration of exercise was recorded with a stopwatch. The work load initially was 50

watts and increased 25 watts every three minutes. The subject was monitored by telemetry with simultaneous leads II and V_5 throughout exercise. An electrocardiogram with simultaneous leads II and V_5 was recorded at the onset of angina pectoris. The heart rate at the onset of angina pectoris was obtained from this electrocardiogram. The blood pressure was recorded at the onset of angina pectoris, with the patient continuing to exercise until the blood pressure was recorded.

In a double-blind, ramdomized, crossover study, each subject then breathed 50 ppm of carbon monoxide for 1 hour on one morning and compressed, purified air for 1 hour on the other morning. The carbon monoxide and compressed, purified air were breathed from a tank through a mask. We used a Bird Mark 7 Respirator, with pressure settings and flow rates reduced and a built-in expiratory leak, so that significant positive pressure was not applied. Eight of the 15 patients breathed carbon monoxide on day 1 and compressed, purified air on day 2. The other seven patients breathed compressed, purified air on day 1 and carbon monoxide on day 2. Analysis of the carbon monoxide inhaled disclosed 50.7 ppm in the first tank used, 50 ppm in the second tank used, and 51.0 ppm in the third tank used.

After the patient breathed carbon monoxide or compressed, purified air for 1 hour, venous blood was drawn and analyzed for carboxyhemoglobin and hemoglobin levels (methemoglobin levels also in the last eight subjects). The subject then sat on the bicycle ergometer and had an electrocardiogram with leads II and V_5 simultaneously recorded. The heart rate was measured from this electrocardiogram. The patient then

exercised upright on the bicycle ergometer until the onset of anginal discomfort, and the duration of exercise was recorded with a stopwatch.

An electrocardiogram with simultaneous leads II and V_5 was recorded at the onset of angina pectoris, with the patient continuing to exercise until the blood pressure was recorded.

The electrocardiograms were analyzed in a blind manner after the study was completed. The data were analyzed with Student's t-test for correlated means.

SECTION 5

RESULTS

Table 1 indicates the code and numbers of each individual patient in the study, his or her age, that coronary artery disease was documented by coronary angiography in all 15 subjects, and which eight subjects had a previously documented healed myocardial infarction. Table 2 shows the randomization code. Table 3 reveals the hemoglobin values during the four different study periods for each individual subject.

Table 4 indicates the individual carboxyhemoglobin values for each subject and the mean ± one standard deviation values during the four different study periods. Table 4 also shows statistical levels of significance. Table 5 shows the individual methemoglobin levels for patients 8-15 during the four different study periods.

Table 6 indicates the individual exercise duration until angina pectoris values for each subject and the mean ± one standard deviation values during the four different study periods. Table 6 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air reduces the exercise duration until the onset of anginal pain.

Table 7 reveals the individual exercise-induced S-T segment depression values for each subject during the four different study periods. For the eight different patients who manifested ischemic S-T segment depression $\geq$ 1.0 mm induced by exercise, table 7 also shows the mean ± one standard

deviation values during the four different study periods. Table 7 also reveals statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air does not significantly affect the amount of ischemic S-T segment depression after exercise-induced angina pectoris. However, ischemic S-T segment depression $\geq$ 1.0 mm after exercise-induced angina pectoris occurred earlier, after less exercise, and at a lower product of systolic blood pressure times heart rate at the onset of angina pectoris at a mean venous carboxyhemoglobin of 2.02% compared to 1.09% (the control period) or compared to after breathing compressed, purified air.

Table 8 indicates the individual resting heart rate values for each subject and the mean ± one standard deviation values during the four different study periods. Table 8 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air does not affect the resting heart rate.

Table 9 indicates the individual resting systolic blood pressure values for each subject and the mean ± one standard deviation values during the four different study periods. Table 9 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing

compressed, purified air does not affect the resting systolic blood pressure.

Table 10 indicates the individual resting diastolic blood pressure values for each subject and the mean ± one standard deviation values during the four different study periods. Table 10 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air does not affect the resting diastolic blood pressure.

Table 11 indicates the individual resting product of systolic blood pressure times heart rate values for each subject and the mean ± one standard deviation values during the four different study periods. Table 11 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air does not affect the resting systolic blood pressure times heart rate (an indirect index of myocardial oxygen demand).

Table 12 indicates the individual heart rate at the onset of angina pectoris values for each subject and the mean ± one standard deviation values during the four different study periods. Table 12 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to

breathing compressed, purified air reduces the heart rate at the onset of angina pectoris.

Table 13 indicates the individual systolic blood pressure at the onset of angina pectoris values for each subject and the mean ± one standard deviation values during the four different study periods. Table 13 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air reduces the systolic blood pressure at the onset of angina pectoris.

Table 14 indicates the individual diastolic blood pressure at the onset of angina pectoris values for each subject and the mean ± one standard deviation values during the four different study periods. Table 14 also reveals statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air increases the diastolic blood pressure at the onset of angina pectoris.

Table 15 indicates the individual product of systolic blood pressure times heart rate at the onset of angina pectoris values for each subject and the mean ± one standard deviation values during the four different study periods. Table 15 also shows statistical levels of significance. These data indicate that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air

reduces the systolic blood pressure times heart rate at the onset of angina pectoris (an indirect index of myocardial oxygen delivery).

TABLE 1. PATIENTS

No.	Code	Age	Coronary Disease Documented by Coronary Angiography	Previous Myocardial Infarction
1	W. P.	65	Yes	No
2	H. J.	58	Yes	No
3	E. B.	68	Yes	No
4	D. L.	49	Yes	Yes
5	E. M.	54	Yes	Yes
6	V. M.	68	Yes	No
7	S. C.	62	Yes	Yes
8	F. B.	62	Yes	Yes
9	H. P.	70	Yes	No
10	E. F.	55	Yes	Yes
11	R. S.	59	Yes	Yes
12	J. P.	56	Yes	No
13	J. F.	61	Yes	No
14	J. T.	45	Yes	Yes
15	E. S.	53	Yes	Yes
Mean		59.0		
SD		±7.2		

TABLE 2. RANDOMIZED CODE

	DAY 1	DAY 2
1	CO	Air
2	Air	CO
3	Air	CO
4	CO	Air
5	CO	Air
6	Air	CO
7	Air	CO
8	Air	CO
9	CO	Air
10	CO	Air
11	Air	CO
12	CO	Air
13	CO	Air
14	Air	CO
15	CO	Air

TABLE 3. HEMOGLOBIN (grams %)

	Air Control	After Air	CO Control	After CO
1	13.8	13.8	13.9	13.8
2	14.9	14.8	14.7	14.8
3	15.6	15.5	15.4	15.5
4	15.9	15.8	15.7	15.8
5	15.6	15.6	15.4	15.3
6	13.7	13.6	13.5	13.6
7	13.8	13.9	13.9	14.0
8	14.9	15.1	15.2	15.0
9	14.6	14.7	14.5	14.6
10	14.7	14.8	14.8	14.7
11	15.1	15.0	15.2	15.1
12	15.8	15.7	15.9	15.8
13	13.7	13.6	13.5	13.6
14	15.7	15.8	16.0	15.9
15	16.2	16.2	16.3	16.3

TABLE 4. COHb (%)

	Air Control	After Air	CO Control	After CO
1	1.1	1.0	1.0	1.9
2	1.2	1.2	1.1	2.0
3	1.2	1.1	1.2	2.1
4	0.9	0.9	0.8	1.9
5	1.0	0.9	1.1	2.1
6	1.3	1.2	1.1	1.9
7	1.3	1.2	1.3	2.3
8	0.8	0.8	1.1	2.2
9	1.1	1.1	1.0	2.0
10	1.0	1.0	0.9	1.8
11	0.9	0.8	1.0	1.9
12	1.0	0.9	1.2	2.0
13	1.2	1.1	1.3	2.1
14	1.0	0.9	1.0	1.8
15	1.1	1.0	1.3	2.3
Mean	1.07	1.00	1.09	2.02
SD	±0.15	±0.14	±0.15	±0.16
			t = 34.749 P < 0.001	

For after CO minus CO control compared to after air minus air control, $t = 43.533$, $P < 0.001$

TABLE 5. METHEMOGLOBIN (%)

	Air Control	After Air	CO Control	After CO
8	0.1	0.1	0.1	0.1
9	0.1	0.1	0.1	0.1
10	0.1	0.1	0.1	0.1
11	0.1	0.1	0.1	0.1
12	0.1	0.1	0.1	0.1
13	0.1	0.1	0.2	0.2
14	0.1	0.1	0.1	0.1
15	0.2	0.2	0.2	0.2

TABLE 6. EXERCISE DURATION UNTIL ANGINA PECTORIS (seconds)

	Air Control	After Air	CO Control	After CO
1	346	362	358	319
2	298	305	291	263
3	372	387	364	339
4	350	341	355	312
5	330	343	337	304
6	324	340	316	289
7	180	193	185	167
8	287	276	271	237
9	222	211	217	188
10	402	419	413	371
11	496	515	479	436
12	453	429	440	392
13	187	200	194	175
14	428	442	419	381
15	193	191	186	165
Mean	324.5	330.3	321.7	289.2
SD	±98.5	±100.7	±96.0	±88.0
	1.8% increase t = 1.645 P - NS		10.1% decrease t = 13.203 P < 0.001	

For after CO minus CO control compared to after air minus air control, t = 10.303, P < 0.001

TABLE 7. EXERCISE-INDUCED S-T DEPRESSION (mm)

	Air Control	After Air	CO Control	After CO
1	0.0	0.0	0.0	0.0
2	1.0	1.0	1.0	1.0
3	0.0	0.0	0.0	0.0
4	1.0	1.0	1.0	1.0
5	1.0	1.0	1.0	1.25
6	2.0	2.0	2.0	2.0
7	0.0	0.0	0.0	0.0
8	1.0	1.0	1.0	1.0
9	3.0	3.0	3.0	3.0
10	0.0	0.0	0.0	0.0
11	1.5	1.5	1.5	1.5
12	0.0	0.0	0.0	0.0
13	1.0	1.0	1.0	1.0
14	0.0	0.0	0.0	0.0
15	0.0	0.0	0.0	0.0
Mean for pts with S-T depression	1.44	1.44	1.44	1.47
SD	±0.73	±0.73	±0.73	±0.71
			P = NS	

For after CO minus CO control compared to after air minus air control, P = NS

TABLE 8. RESTING HEART RATE (beats/min)

	Air Control	After Air	CO Control	After CO
1	54	58	55	55
2	82	78	78	74
3	59	59	67	64
4	80	72	76	80
5	70	74	80	78
6	65	60	60	56
7	67	65	59	59
8	64	59	56	55
9	63	63	64	67
10	85	86	70	67
11	78	77	84	85
12	63	55	50	60
13	54	52	50	48
14	80	76	84	78
15	64	65	67	63
Mean	68.5	66.6	66.7	65.9
SD	±10.1	±9.9	±11.7	±10.9
			P = NS	

For after CO minus CO control compared to after air minus air control, P = NS

TABLE 9. RESTING SYSTOLIC BLOOD PRESSURE (mm Hg)

	Air Control	After Air	CO Control	After CO
1	114	110	110	112
2	130	128	132	130
3	118	116	116	118
4	126	124	130	128
5	126	124	122	120
6	122	124	126	128
7	130	124	132	128
8	128	130	120	122
9	134	138	138	136
10	128	130	132	134
11	128	124	122	120
12	120	120	122	120
13	134	132	138	136
14	140	136	134	134
15	130	126	128	126
Mean	127.2	125.7	126.8	126.1
SD	±6.7	±7.2	±8.1	±7.3
			P = NS	

For after CO minus CO control compared to after air minus air control, P = NS

TABLE 10. RESTING DIASTOLIC BLOOD PRESSURE (mm Hg)

	Air Control	After Air	CO Control	After CO
1	72	70	70	72
2	80	82	82	80
3	76	74	72	74
4	80	78	84	84
5	80	78	76	74
6	80	78	84	84
7	82	80	80	78
8	82	84	76	74
9	86	86	88	90
10	88	88	90	90
11	86	84	84	84
12	72	70	74	76
13	80	78	82	80
14	90	88	86	88
15	82	80	84	84
Mean	81.1	79.9	80.8	80.8
SD	±5.2	±5.7	±5.9	±6.0
			P = NS	

For after CO minus CO control compared to after air minus air control, P = NS

TABLE 11. RESTING SYSTOLIC BLOOD PRESSURE TIMES HEART RATE

	Air Control	After Air	CO Control	After CO
1	6,156	6,380	6,050	6,160
2	10,660	9,984	10,296	9,620
3	6,962	6,844	7,772	7,552
4	10,080	8,928	9,880	10,240
5	8,820	9,176	9,760	9,360
6	7,930	7,440	7,560	7,168
7	8,710	8,060	7,788	7,552
8	8,192	7,670	6,720	6,710
9	8,442	8,694	8,832	9,112
10	10,880	11,180	9,240	8,978
11	9,984	9,548	10,248	10,200
12	7,560	6,600	6,100	7,200
13	7,236	6,864	14,608	13,284
14	11,200	10,336	11,256	10,452
15	8,320	8,190	8,576	7,938
Mean	8,742	8,393	8,979	8,768
SD	±1,521	±1,463	±2,216	±1,859
			P = NS	

For after CO minus CO control compared to after air minus air control, P = NS

TABLE 12. HEART RATE AT ANGINA (beats/min)

	Air Control	After Air	CO Control	After CO
1	82	84	84	84
2	116	116	116	104
3	94	94	97	91
4	112	116	120	104
5	104	112	104	100
6	100	108	100	97
7	91	91	88	88
8	111	108	108	97
9	125	120	120	112
10	111	115	107	101
11	125	125	124	116
12	100	107	91	91
13	84	88	88	82
14	97	100	100	100
15	88	86	82	78
Mean	102.7	104.7	101.9	96.3
SD	±13.8	±13.3	±13.8	±10.8
			t = 4.483 P < 0.001	

For after CO minus CO control compared to after air minus air control, $t = 5.638$, $P < 0.001$

TABLE 13. SYSTOLIC BLOOD PRESSURE AT ANGINA (mm Hg)

	Air Control	After Air	CO Control	After CO
1	184	182	182	176
2	178	180	178	174
3	172	176	174	170
4	186	188	188	182
5	166	170	168	164
6	186	190	188	182
7	164	168	166	162
8	186	184	182	176
9	192	190	190	186
10	194	198	196	192
11	174	178	172	170
12	188	186	186	182
13	168	168	166	162
14	198	202	196	192
15	176	174	176	170
Mean	180.8	182.3	180.5	176.0
SD	±10.6	±10.3	±10.1	±9.9

$t = 14.788$
$P < 0.001$

For after CO minus CO control compared to after air minus air control, $t = 9.268$, $P < 0.001$

TABLE 14. DIASTOLIC BLOOD PRESSURE AT ANGINA (mm Hg)

	Air Control	After Air	CO Control	After CO
1	78	78	78	80
2	90	88	88	92
3	82	80	78	82
4	86	84	90	92
5	86	84	84	82
6	84	84	88	90
7	90	90	86	84
8	90	86	80	82
9	90	88	92	94
10	90	92	94	96
11	88	84	86	88
12	76	74	80	82
13	86	82	90	88
14	94	90	92	94
15	84	82	88	90
Mean	86.3	84.4	86.3	87.7
SD	±4.9	±4.9	±5.2	±5.3
			t = 2.954 P < 0.025	

For after CO minus CO control compared to after air minus air control, t = 5.000, P < 0.001

TABLE 15. SYSTOLIC BLOOD PRESSURE TIMES HEART RATE AT ANGINA

	Air Control	After Air	CO Control	After CO
1	15,088	15,288	15,288	14,784
2	20,648	20,880	20,648	18,096
3	16,168	16,544	16,878	15,470
4	20,832	21,808	22,560	18,928
5	17,264	19,040	17,472	16,400
6	18,600	20,520	18,800	17,654
7	14,924	15,288	14,608	14,256
8	20,646	19,872	19,656	17,072
9	24,000	22,800	22,800	20,832
10	21,534	22,770	20,972	19,392
11	21,750	22,250	21,328	19,720
12	18,800	19,902	16,926	16,562
13	14,112	14,784	14,608	13,284
14	19,206	20,200	19,600	19,200
15	15,488	14,964	14,432	13,260
Mean	18,604	19,127	18,438	16,994
SD	±2,986	±2,969	±2,923	±2,407
	+2.8%		-7.8%	

t = 5.972
P < 0.001

For after CO minus CO control compared to after air minus air control, t = 6.768, P < 0.001

SECTION 6

DISCUSSION

These data show that breathing carbon monoxide to raise the mean venous carboxyhemoglobin level from 1.09% to 2.02% in comparison to the control period or in comparison to breathing compressed, purified air does not affect the resting product of systolic blood pressure times heart rate (an indirect index of myocardial oxygen demand), reduces the product of systolic blood pressure times heart rate at the onset of angina pectoris (an indirect index of myocardial oxygen delivery), and reduces the exercise duration until the onset of anginal pain. Ischemic S-T segment depression $\geq$ 1.0 mm after exercise-induced angina pectoris occurs earlier, after less exercise, and at a lower product of systolic blood pressure times heart rate at the onset of angina pectoris at a mean venous carboxyhemoglobin level of 2.02% compared to 1.09% (the control period) or compared to after breathing compressed, purified air.

The significance of these data obtained in a double-blind, randomized, crossover study is that a 2% venous carboxyhemoglobin level aggravates angina pectoris. This information should be considered in setting the national air quality criteria for carbon monoxide. These data also indicate that if there is a safe threshold of carbon monoxide exposure for patients with angina pectoris due to coronary artery disease, this level would have to be very low.

There are millions of persons in the U.S.A. with stable angina pectoris who are susceptible to adverse health effects from low levels of carbon monoxide exposure. A 10% reduction in exercise tolerance

until angina pectoris at a 2% venous carboxyhemoglobin level is clinically important and may precipitate anginal pain during activities which could be performed without developing anginal pain at a 1% venous carboxyhemoglobin level.

Patients with unstable angina pectoris or acute myocardial infarction are also more susceptible than patients with stable angina pectoris to adverse effects from low levels of carbon monoxide exposure. The more critical the coronary artery disease, the more susceptible is the individual to adverse health effects from low levels of carbon monoxide exposure. Low levels of carbon monoxide exposure may contribute to myocardial infarction and to death in these persons. In addition, nearly 25% of persons dying suddenly from coronary heart disease have had no prior recognized symptoms of heart disease.

Therefore, on the basis of the medical data from this research study, there should be no relaxation of the present U.S. Environmental Protection Agency Air Quality Criteria for Carbon Monoxide.

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